Remarks

Claims 1, 5, 7, 12, 17, 21, 23, 28, 33, 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, and 119-201 were previously and are still pending in this application.

Applicant would like to thank Examiners Niloofar Rahmani and Margaret Seaman for discussing the FINAL Office Action with Applicant's representatives Edward Gates and Roque El-Hayek during a telephone interview ("interview") on November 2, 2006. The outstanding rejections in the instant application were discussed. The substance of the discussion is reflected in the remarks and arguments presented below.

Allowable Claims

Applicant respectfully requests clarification of the record. In the Office Actions dated 1/13/04 and 10/20/04, claims 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, 143-187 were "allowed". In addition, claims 28, 122, 127, 132, 133, 137 and 138 were "objected to" only as being dependent on a rejected base claim, but allowable if rewritten in independent form. In the Office Actions dated 12/12/2005 and 8/11/2006 the status of these allowed" and "objected to" claims appears to have been mistakenly overlooked. No new rejections of these claims were presented but, instead, all the claims were rejected instead and the obviousness rejections of record were "maintained". This appears to be an error, as there is no outstanding rejection of the previously allowed claims. Applicant assumes that the inclusion of the previously allowed claims in the rejection was an oversight. This issue was discussed during the interview with the Examiners. Examiner Seaman agreed that the inclusion of the previously allowed claims in the rejection was an oversight. Accordingly, Examiner Seaman indicated that the Finality of the Office Action will be withdrawn and the status of the previously allowed claims will be re-considered.

Rejections Under 35 U.S.C. §103

The rejection of claims 1, 5, 7, 12, 17, 21, 23, 33, 119-121, 123-126, 128-131, 134-136, 139-142, and 188-201 under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al., Kataoka et al., and Rentsch et al. was maintained in the Final Office Action "for reasons of record". The

Examiner asserted that the Declaration of Dr. Bathasar is Opinion Declaration and "is insufficient to overcome the rejection of the claims based upon 35 U.S.C. 103(a)" and that "[n]o weight is given to an opinion on the ultimate legal conclusion in issue." (Citing *In re Lindall*,155 USPQ 521 and *In re Chilowsky*, 134 USPQ 515).

Applicant respectfully traverses the rejection and requests reconsideration. Arguments presented in the response dated June 12, 2006 are reiterated here. Applicant believes the rejection under 35 U.S.C. 103 is improper because: (1) the Examiner has not met the burden of making a *prima facie* case of obviousness, (2) the cited references, taken together, actually teach away from the claimed invention, (3) there is additional prior art of record (US patent 5,580,899, Mayhew et al.) discussed below that teaches away from the claimed invention.

Kataoka et al. teach away from the claimed invention. The Kataoka et al. reference shows comparative data on a fatty acid conjugate versus the parent compound. Kataoka et al. show an experiment involving a fatty acid-anti cancer drug conjugate, N4-behenoyl-Ara-C. The conjugate was given at a dose of 100-1000 mg/kg, IP (Kataoka et al., page 149, lines 6-7). This was then contrasted with the parent compound, Ara-C, which was reported to be given at a dosage of 1600 mg/kg IP (Kataoka et al., page 149, lines 44-45). Clearly, the conjugate (N4-behenoyl-Ara-C) was given at a ***lower*** dose than the parent compound (Ara-C). The fact that the 1600 mg/kg dose of the parent compound used in the model was tolerated by the mice (because the mice did not die) suggests that this latter dose was either at or below the MTD of Ara-C in this model. Thus, Kataoka et al. does not teach administering a fatty acid conjugate at a dose *above* the MTD of the parent compound but, instead, teach administering a fatty acid conjugate at a dose *below* the MTD of the parent. This is the opposite of that required by the claimed invention. Therefore, it is not possible to conclude from Kataoka et al. that a conjugate should be given at a dose above the MTD of the parent compound, as claimed. Accordingly, not only there is no basis in Kataoka et al. for a *prima facie* case for rejecting the claims but, in fact, Kataoka at al. teach away from the claimed invention.

The Examiner's theory of obvious is not credible in view of the references of record. In the prior Office Action addressing the rejection on the basis of Kataoka et al., the Examiner stated that Kataoka et al. teaches that "the fatty acid endows Ara-C with hydrophobicity and, thus, enables BH-AC to be released slowly in the body and would circulate in the body for a

prolonged period of time." From this the Examiner concluded that a *higher* dose of conjugate would be suggested. Such a conclusion, however, is not credible and is wholly unsupported by the references of record, including the Kataoka et al. reference itself.

Kataoka et al. administered the conjugate at a ***lower*** dose than the parent. This confirms what one of ordinary skill in the art would have expected, that is, if the drug circulates for a longer period, then ***less*** drug would be needed. The Examiner's reasoning therefore is not credible as it is contradicted within the Kataoka et al. reference itself.

The Examiner's conclusion is contradicted by other scientific literature, as well. Dr. Balthasar provided examples from the literature that demonstrated that slow release of anti-cancer drugs, where the time-course of drug circulation is prolonged, can actually decrease the MTD. One example cited by Dr. Balthasar was a review by Rowinsky and Verweij of phase I clinical studies with topotecan. Rowinsky and Verweij cited data showing that the MTD of topotecan is 22.5 $mg/m^2/d$ when released into the body over 30 min, but is 1 $mg/m^2/d$ when released into the body over 72 hours (Rowinsky EK and Verweij J, Review of phase I clinical studies with topotecan, Seminars in Oncology, 24: S20-3-S20-10, 1997). The MTD was ***lower*** when the drug was administered more slowly. Thus, ***less*** drug had to be administered when the drug was administered more slowly. The result is additional evidence that contradicts the Examiner's reasoning and renders the Examiner's position not credible.

US patent 5,580,899 (Mayhew et al.) also teaches away from the claimed invention. Mayhew et al., teach that the administration of less, not more, of the fatty acid conjugated drug versus the parent drug. Mayhew et al., specifically teach administering the fatty acid conjugated drugs described in Mayhew et al., in amounts that are the same as or ***less*** than the amounts used when administering the unconjugated anticancer compounds (See column 9, lines 50-67 and column 12, lines 52-67). Mayhew et al., make it clear that the dose of the fatty acid conjugated drug would have been expected to be a reduced dose compared to the dose of the unconjugated drug. Thus, Mayhew et al., teach away from a main feature of the present invention, that is, the administration of anticancer compounds as conjugates in amounts which exceed the MTD of the unconjugated anticancer compound.

A more recent example provided by Dr. Balthasar was from Dr. Balthasar's work showing that slowing the time course of drug administration *decreases* MTD. In recent work conducted in Dr. Balthasar's laboratory (Lobo ED and Balthasar JP, Pharmacokinetic-pharmacodynamic modeling of methotrexate-induced toxicity in mice, Journal of Pharmaceutical Sciences, 92: 1654-1664, 2003), toxicity induced by methotrexate following intra-peritoneal administration in mice was investigated. The MTD of methotrexate was highly dependent on the time-course of release of the drug. Following administration of methotrexate by rapid ("bolus") injection, the authors found that MTD was 760 mg/kg. Following slow release of the dose from an osmotic pump over 72 hours, they found that MTD was dramatically reduced to 3.8 mg/kg. Again, ***less*** drug had to be administered when the drug was administered more slowly. This is not merely "opinion" evidence which can be dismissed. This is published data which again contradicts and renders not credible the Examiner's reasoning.

The remaining cited references do not undermine or contradict the teaching away from the invention. The Applicant's representatives discussed during the interview the following point about which agreement was not reached. Applicant's representatives noted that MTD was dependent on the mode of administration. Applicant's representatives noted that the remaining references of record were silent as to whether MTD of a conjugate was decreased relative to the MTD of the parent. Applicant's representatives, however, noted that the "Ara-C" discussed in the remaining references (Yoshida et al. and Rentsch et al.) was the same "Ara-C" compound discussed in Kataoka et al. In view of this, it is believed that the Examiner has no credible reason to assert that the prior art suggests a conjugate of Ara-C will have a higher MTD than the parent Ara-C, when such a conjugate was in fact actually tested and found to have a lower MTD than the parent Ara-C.

Yoshida et al. investigated the administration of a fatty acid conjugate of the compound Ara-C (the same parent compound that was investigated by Kataoka et al.). The fatty acid conjugate of Ara-C (BH-AC) was administered at doses ranging from 500 mg/m^2 to 1300 mg/m^2 by intravenous (IV) drip in 10 patients diagnosed with non-Hodgkin's lymphoma. The dose levels (500, 700, 900, and 1300 mg/m^2) were administered to groups of three patients on a 5-consecutive day schedule. Yoshida et al. did not investigate toxicity resulting from the

administration of the parent compound (Ara-C), nor did Yoshida et al. provide pharmacokinetic data on Ara-C administered IV. As such, this reference does not provide a comparison of the MTD of the conjugate versus Ara-C in this treatment group via this mode of administration. However, Yoshida et al. refer to prior art administrations of the parent Ara-C as high as 3 g/m^2 (3,000 mg/m^2, q 12 hours, days -7 to -4; from Champlin et al., Seminars in Oncology, Vol. XII, No. 2, supplement 3, 1985, pages 190-195, cited in Yoshida et al. on page 1823, first paragraph of right-hand column). Clearly, 1300mg/m^2 is lower than 3000mg/m^2.

Rentsch et al. studied 4-N-octadecyl-Ara-C, an alkylated derivative of Ara-C bearing a saturated C18 alkyl group on the Ara-C 4-amino group (not a fatty acid conjugate). This reference discloses no comparative data on dose levels of 4-N-octadecyl-Ara-C relative to dose levels of Ara-C in mice. Rentsch et al. did not investigate the development of toxicity following the administration of Ara-C and/or following administration of the alkylated derivative of Ara-C. Consequently, the teachings of Rentsch et al. do not allow making conclusions about the MTDs of Ara-C and/or the conjugates of Ara-C.

Applicant asserted at the interview that it is the Examiner's burden to present a reference(s) upon which a *prima facie* rejection can be based. The cited references do not represent such a reference(s), particularly when taken together with all the references of record which teach away from the invention. The Examiner should not, and cannot not under the law, ignore the prior art as a whole.

In summary, it is clear that none of the references (cited and/or of record) teach or suggest the main and novel feature of the instant invention. On the contrary, the references teach away from the claimed invention. It is not possible to conclude from the cited art that one can administer a conjugate at a dose higher than the MTD of the parent compound. Moreover, the only reason advanced for rejecting the claims is contradicted by the prior art of record. It, therefore, is believed that the Examiner has not made out a *prima facie* case for rejecting the claims. Even if a *prima facie* case had been made out previously, that case had been convincingly rebutted.

In view of the foregoing, applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 103.

Rejection on the Basis of Obviousness-type Double Patenting

The Examiner maintains the rejection of claims 1, 5, 7, 12, 17, 21, 23, 28, 33, 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, 119-201 on the basis of obviousness-type double patenting over claim 7 of U.S. 6,602,902 ('902 patent) because the claims are "fully embraced" by claim 7 of the '902 patent. According to the Examiner, the prior art claim is a species of the instant claims. The Examiner asserts that "[o]n column 5, lines 19-25 of '902 the pharmaceutical agent is an anti-cancer agent included especially taxanes e.g., Taxol and Taxotere. On columns 7-8, Example 1, conjugate 1 and on columns 9-10, Example 2, conjugate 2 are some examples of covalent conjugate of cis-docosahexanoic [*sic*] acid and a noncentral nervous system active agent. The Examiner asserts that "[s]ince the prior art does not mention the MTD, then it is inherently there."

Applicant respectfully traverses the rejection for the following reasons.

The Examiner applied the incorrect test for obviousness-type double patenting.

Section 804 of the MPEP states (emphasis added):

> "In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is - ***does any claim in the application define an invention that is merely an obvious variation of an invention claimed in the patent?*** If the answer is yes, then an "obviousness-type" nonstatutory double patenting rejection may be appropriate. ***Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed*** in a commonly owned patent>, or a non-commonly owned patent but subject to a joint research agreement as set forth in 35 U.S.C. 103(c)(2) and (3),< when the issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent. See *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 58 USPQ2d *>1869< (Fed. Cir. 2001); *Ex parte Davis*, 56 USPQ2d 1434, 1435-36 (Bd. Pat. App. & Inter. 2000)."

Thus, the test for obviousness-type double patenting of the instant claims is whether the pending claims would have been "obvious" or "not patentably distinct" over issued claim 7. The test is not whether the pending claims would infringe or be "embraced by" the issued claim as asserted by the Examiner.

The present claims are not even a species of the prior art claim 7.

Claim 7 of the '902 patent is directed to a pharmaceutical preparation of a covalent conjugate of cis-docosahexanoic acid and a *noncentral nervous system active agent*. The '902 patent defines a noncentral nervous system active agents as agents that "have no function or use within the central nervous system."

Claims in the instant application are directed to formulations, methods and compositions for administering fatty acid-anticancer agents. Anticancer agents are commonly used to treat cancers within the central nervous system. Thus, anticancer agents are not "noncentral nervous system active agents" as defined by the '902 patent. Therefore, claim 7 of the '902 patent does not even embrace the anticancer agents of instant claims as asserted by the Examiner.

The Examiner has not made out a *prima facie* case for rejecting the claims on the basis of obviousness-type double patenting.

Section 804 of the MPEP states (emphasis added):

> ***"[A]ny analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination.*** *In re Braat*, 937 F.2d 589, 19 USPQ2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).
> Since the analysis employed in an obviousness-type double patenting determination parallels the guidelines for a 35 U.S.C. 103(a) rejection, the factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are employed when making an obvious-type double patenting analysis.
>
> ***Any obviousness-type double patenting rejection should make clear:***
> ***(A) The differences between the inventions defined by the conflicting claims - a claim in the patent compared to a claim in the application; and***
> ***(B) The reasons why a person of ordinary skill in the art would conclude that the invention defined in the claim*** **>at issue would have been< an obvious variation of the invention defined in a claim in the patent."

The Examiner has not identified the differences between the pending claims and the prior art and explained why those differences would have been obvious to one of ordinary skill in the

art at the time of the invention. Accordingly, the Examiner has not made out a *prima facie* case for rejecting the claims on the basis of obviousness-type double patenting.

Surprising results support the nonobviousness of the claimed invention. An aspect of the invention involves the unexpected finding that higher concentrations of anticancer drugs can be delivered to human subjects than ever expected before. The dose-limiting toxicity of the anticancer drug is altered due to its conjugation to the fatty acid. This has important implications on anticancer therapies.

As set forth at page 12, lines 5-9, the MTD of paclitaxel in humans is 225 mg/m^2. This is well-known as paclitaxel is clinically approved and has been used in thousands of cancer patients. As set forth at page 14, the MTD of the conjugate DHA-paclitaxel is 4-5 times greater by weight in the subjects tested. This would mean a predicted dose in humans based on the present disclosure of 900-1125 mg/m^2 (4-5 times 225 mg/m^2). It is noted that 1125 mg/m^2 is completely unexpected as a dosage for humans.

Remarkably, even at this high dose, the patients did not experience hair loss and some of the other side effects characteristic of unconjugated paclitaxel. Thus, a surprising aspect of the invention is the ability to increase the dose yet reduce the side effects. These results were presented at the "2000 International Symposium on Tumor-Targeted Delivery Systems" held in Bethesda, Maryland in September of 2000. These results also were presented at CapCure, in September of 2000 and at the Gordon Research Conference entitled "Chemotherapy of Experimental Clinical Cancer" held at Oxford University, UK, in September, 2000. A copy of the September 2000 presentations was submitted to USPTO with a response filed on October 30, 2000.

The MTD of numerous fatty acid-anticancer drug conjugates, according to the invention, has been tested in rodents. Among them are camptothecin, podophyllotoxin, doxorubicin, and epothilone D. The conjugates consistently had MTDs greater than the MTD of the unconjugated drug, and in some cases, greater than six times the MTD of the unconjugated drug. Such a result, consistent with the teaching of the present invention, simply was not remotely predictable.

Another surprising aspect of the invention is the ability to solubilize much higher concentrations of the conjugates of the invention in surfactants such as polyoxyethylated castor

oils than is possible for anticancer compounds which are not conjugated to fatty acids. For example, applicant can routinely obtain 40 mg/ml or more of the docosahexaenoic acid-paclitaxel conjugate in a 50%/50% Cremaphor/ethanol co-solvent system, whereas the prior art typically is at 6 mg/ml of paclitaxel in the same co-solvent system.

Another surprising aspect of the invention is the ability to dissolve conjugates of taxanes and fatty acids in ethanol at very high concentrations, e.g., 100 mg/ml. The conjugates are very stable when stored in ethanol in that manner.

The foregoing unexpected results are embraced by the rejected claims. The instant claims describe injectable formulations, methods and compositions for administering a fatty acid-anticancer compound in an amount that is much greater than the maximum tolerated dose for the unconjugated anticancer compound. Each independent claim in the instant application includes at least one limitation that is not present in the prior art or obvious from the prior art. The Examiner has not considered, identified or addressed such limitations, and, as such, has not made out a *prima facie* basis for rejecting the claims.

The Examiner has not addressed the unexpected results detailed in the application.

Applicant believes that the Examiner has overlooked the unexpected results described in the application. The specific issues of obviousness, assuming a *prima facie* case has been made out, is whether there is a sufficient showing to rebut such a *prima facie* case. It is applicant's position that even if a *prima facie* case has been made, which the applicant disputes for the reasons stated above, the applicant's claimed compositions and related methods result in biological activities which were unexpected and which could not have been predicted by those of ordinary skill in the art. These unexpected results are persuasive evidence that applicant's claimed compositions have non-obvious properties. Since a claimed composition and its properties are inseparable in patent law, the claimed composition and related methods would not have been obvious at the time the invention was made to a person having ordinary skill in the art.

The Court of Appeals for the Federal Circuit has stated that "when an Applicant demonstrates certain results and states that those results were unexpected, it should suffice to establish unexpected results to rebut a finding of obviousness in the absence of evidence to the contrary. *In re Soni,* 54 F3d 746 (Fed. Cir. 1995). The Examiner has not provided any basis to

question the applicant's statements about unexpected properties. Accordingly, there is no reasonable basis to doubt that applicant has established unexpected results for the claimed compounds and related methods.

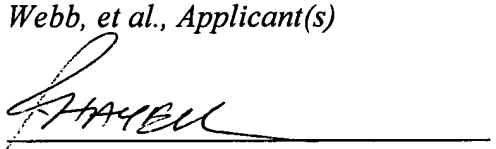
In view of the above arguments withdrawal of the rejection of the claims on the basis of obviousness-type double patenting is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

A one-month extension of time, from August 11, 2006 to November 30, 2006, is requested for response to the Office Action mailed from the Patent Office on December 12, 2005. A check in the amount of $120.00 is enclosed for said extension. If there is any additional fee occasioned by this response, including any additional extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Webb, et al., Applicant(s)

By: 

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